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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:30:40 ON 21 JUL 2006

=> fil .bec
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 13:30:56 ON 21 JUL 2006
ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

11 FILES IN THE FILE LIST

=> s thymidylate synthase#
FILE 'MEDLINE'
          4250 THYMIDYLATE
         94997 SYNTHASE#
L1        3500 THYMIDYLATE SYNTHASE#
                 (THYMIDYLATE(W)SYNTHASE#)

FILE 'SCISEARCH'
          4767 THYMIDYLATE
        111609 SYNTHASE#
L2        3595 THYMIDYLATE SYNTHASE#
                 (THYMIDYLATE(W)SYNTHASE#)

FILE 'LIFESCI'
          1034 "THYMIDYLATE"
         24583 SYNTHASE#
L3         745 THYMIDYLATE SYNTHASE#
                 ("THYMIDYLATE"(W)SYNTHASE#)

FILE 'BIOTECHDS'
           192 THYMIDYLATE
          6270 SYNTHASE#
L4         146 THYMIDYLATE SYNTHASE#
                 (THYMIDYLATE(W)SYNTHASE#)

FILE 'BIOSIS'
          5168 THYMIDYLATE
        102303 SYNTHASE#
L5        3169 THYMIDYLATE SYNTHASE#
                 (THYMIDYLATE(W)SYNTHASE#)

FILE 'EMBASE'
          4102 "THYMIDYLATE"
         93596 SYNTHASE#
L6        3466 THYMIDYLATE SYNTHASE#
                 ("THYMIDYLATE"(W)SYNTHASE#)

FILE 'HCAPLUS'
          5542 THYMIDYLATE
         98034 SYNTHASE#
L7        3262 THYMIDYLATE SYNTHASE#
                 (THYMIDYLATE(W)SYNTHASE#)

FILE 'NTIS'
            19 THYMIDYLATE
           238 SYNTHASE#
L8            4 THYMIDYLATE SYNTHASE#
                 (THYMIDYLATE(W)SYNTHASE#)
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FILE 'ESBIOBASE'
          1457 THYMIDYLATE
         46141 SYNTHASE#
L9        1234 THYMIDYLATE SYNTHASE#
                 (THYMIDYLATE(W)SYNTHASE#)

FILE 'BIOTECHNO'
          1423 THYMIDYLATE
         29457 SYNTHASE#
L10       1155 THYMIDYLATE SYNTHASE#
                 (THYMIDYLATE(W)SYNTHASE#)

FILE 'WPIDS'
           209 THYMIDYLATE
          5172 SYNTHASE#
L11        144 THYMIDYLATE SYNTHASE#
                 (THYMIDYLATE(W)SYNTHASE#)

TOTAL FOR ALL FILES
L12      20420 THYMIDYLATE SYNTHASE#

=> s (l12 or ts)(3a)bind?
FILE 'MEDLINE'
         11705 TS
        817701 BIND?
L13        239 (L1 OR TS)(3A)BIND?

FILE 'SCISEARCH'
         13037 TS
        771965 BIND?
L14        186 (L2 OR TS)(3A)BIND?

FILE 'LIFESCI'
          4269 TS
        264647 BIND?
L15          87 (L3 OR TS)(3A)BIND?

FILE 'BIOTECHDS'
           907 TS
         53961 BIND?
L16          29 (L4 OR TS)(3A)BIND?

FILE 'BIOSIS'
         12117 TS
        726724 BIND?
L17        244 (L5 OR TS)(3A)BIND?

FILE 'EMBASE'
         10116 TS
        711625 BIND?
L18        210 (L6 OR TS)(3A)BIND?

FILE 'HCAPLUS'
         24526 TS
       1187375 BIND?
L19        393 (L7 OR TS)(3A)BIND?

FILE 'NTIS'
          1008 TS
         15652 BIND?
L20           0 (L8 OR TS)(3A)BIND?

FILE 'ESBIOBASE'
          4201 TS
        295869 BIND?
```

```
L21         112 (L9 OR TS)(3A)BIND?

FILE 'BIOTECHNO'
          3893 TS
         294519 BIND?
L22         116 (L10 OR TS)(3A)BIND?

FILE 'WPIDS'
          6701 TS
         304983 BIND?
L23          44 (L11 OR TS)(3A)BIND?

TOTAL FOR ALL FILES
L24        1660 (L12 OR TS)(3A) BIND?

=> s inhibit?(5a)(screen? or assay? or detect?)
FILE 'MEDLINE'
        1269810 INHIBIT?
         275166 SCREEN?
         536942 ASSAY?
         960115 DETECT?
L25       21169 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)

FILE 'SCISEARCH'
        1061091 INHIBIT?
         240360 SCREEN?
         400561 ASSAY?
        1095303 DETECT?
L26       16944 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)

FILE 'LIFESCI'
         341476 INHIBIT?
          61519 SCREEN?
         170368 ASSAY?
         286106 DETECT?
L27        8871 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)

FILE 'BIOTECHDS'
          59638 INHIBIT?
          47676 SCREEN?
          31939 ASSAY?
          70206 DETECT?
L28        5468 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)

FILE 'BIOSIS'
        1356821 INHIBIT?
         228540 SCREEN?
         518632 ASSAY?
        1043178 DETECT?
L29       24747 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)

FILE 'EMBASE'
        1157405 INHIBIT?
         306692 SCREEN?
         484026 ASSAY?
         892543 DETECT?
L30       19749 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)

FILE 'HCAPLUS'
        1846698 INHIBIT?
         320076 SCREEN?
         526062 ASSAY?
        1586984 DETECT?
L31       36298 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)
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FILE 'NTIS'
         21190 INHIBIT?
         26235 SCREEN?
         10582 ASSAY?
        140007 DETECT?
L32        417 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)

FILE 'ESBIOBASE'
        472331 INHIBIT?
         91682 SCREEN?
        194970 ASSAY?
        370685 DETECT?
L33      11017 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)

FILE 'BIOTECHNO'
        301415 INHIBIT?
         66678 SCREEN?
        231380 ASSAY?
        290318 DETECT?
L34       9696 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)

FILE 'WPIDS'
        253612 INHIBIT?
        293770 SCREEN?
         50260 ASSAY?
       1106575 DETECT?
L35      11431 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)

TOTAL FOR ALL FILES
L36     165807 INHIBIT?(5A)(SCREEN? OR ASSAY? OR DETECT?)

=> s l24 and l36
FILE 'MEDLINE'
L37           7 L13 AND L25

FILE 'SCISEARCH'
L38           4 L14 AND L26

FILE 'LIFESCI'
L39           3 L15 AND L27

FILE 'BIOTECHDS'
L40           1 L16 AND L28

FILE 'BIOSIS'
L41           9 L17 AND L29

FILE 'EMBASE'
L42           7 L18 AND L30

FILE 'HCAPLUS'
L43           7 L19 AND L31

FILE 'NTIS'
L44           0 L20 AND L32

FILE 'ESBIOBASE'
L45           5 L21 AND L33

FILE 'BIOTECHNO'
L46           2 L22 AND L34

FILE 'WPIDS'
L47           2 L23 AND L35
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TOTAL FOR ALL FILES
L48         47 L24 AND L36

=> s translat?(10a)(regulat? or modulat? or control? or activat? or inhibt?)
FILE 'MEDLINE'
        108139 TRANSLAT?
        826267 REGULAT?
        235430 MODULAT?
       2137122 CONTROL?
        778476 ACTIVAT?
            95 INHIBT?
L49      12736 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

FILE 'SCISEARCH'
        113427 TRANSLAT?
        719265 REGULAT?
        338539 MODULAT?
       1659468 CONTROL?
        878918 ACTIVAT?
            88 INHIBT?
L50      13726 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

FILE 'LIFESCI'
         39155 TRANSLAT?
        274094 REGULAT?
         82167 MODULAT?
        372974 CONTROL?
        242512 ACTIVAT?
            58 INHIBT?
L51       7032 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

FILE 'BIOTECHDS'
         10060 TRANSLAT?
         32876 REGULAT?
         16954 MODULAT?
         62388 CONTROL?
         29828 ACTIVAT?
            26 INHIBT?
L52       1342 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

FILE 'BIOSIS'
         94066 TRANSLAT?
        861129 REGULAT?
        268477 MODULAT?
       2001441 CONTROL?
        789175 ACTIVAT?
           422 INHIBT?
L53      14730 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

FILE 'EMBASE'
         78565 TRANSLAT?
        682459 REGULAT?
        226849 MODULAT?
       3069835 CONTROL?
        694871 ACTIVAT?
           188 INHIBT?
L54      13077 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

FILE 'HCAPLUS'
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        758441 TRANSLAT?
        974260 REGULAT?
        344544 MODULAT?
       2239785 CONTROL?
       1279044 ACTIVAT?
           309 INHIBT?
L55      32909 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

FILE 'NTIS'
         74835 TRANSLAT?
         86479 REGULAT?
         21957 MODULAT?
        331632 CONTROL?
         28891 ACTIVAT?
             4 INHIBT?
L56       2136 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

FILE 'ESBIOBASE'
         55904 TRANSLAT?
        429038 REGULAT?
        121851 MODULAT?
        575788 CONTROL?
        345990 ACTIVAT?
            30 INHIBT?
L57       9230 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

FILE 'BIOTECHNO'
         40022 TRANSLAT?
        271996 REGULAT?
         58358 MODULAT?
        620701 CONTROL?
        233622 ACTIVAT?
            52 INHIBT?
L58       7713 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

FILE 'WPIDS'
         50594 TRANSLAT?
        395109 REGULAT?
        178592 MODULAT?
       2646625 CONTROL?
        273655 ACTIVAT?
            68 INHIBT?
L59       6254 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

TOTAL FOR ALL FILES
L60     120885 TRANSLAT?(10A)(REGULAT? OR MODULAT? OR CONTROL? OR ACTIVAT? OR
               INHIBT?)

=> s l12 and l60
FILE 'MEDLINE'
L61          34 L1 AND L49

FILE 'SCISEARCH'
L62          53 L2 AND L50

FILE 'LIFESCI'
L63          21 L3 AND L51

FILE 'BIOTECHDS'
L64           0 L4 AND L52
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FILE 'BIOSIS'
L65         42 L5 AND L53

FILE 'EMBASE'
L66         42 L6 AND L54

FILE 'HCAPLUS'
L67         50 L7 AND L55

FILE 'NTIS'
L68          0 L8 AND L56

FILE 'ESBIOBASE'
L69         22 L9 AND L57

FILE 'BIOTECHNO'
L70         24 L10 AND L58

FILE 'WPIDS'
L71          1 L11 AND L59

TOTAL FOR ALL FILES
L72        289 L12 AND L60

=> s (l48 or l72) not 2004-2006/py
FILE 'MEDLINE'
       1580187 2004-2006/PY
                (20040000-20069999/PY)
L73         34 (L37 OR L61) NOT 2004-2006/PY

FILE 'SCISEARCH'
       2890216 2004-2006/PY
                (20040000-20069999/PY)
L74         43 (L38 OR L62) NOT 2004-2006/PY

FILE 'LIFESCI'
        234551 2004-2006/PY
L75         23 (L39 OR L63) NOT 2004-2006/PY

FILE 'BIOTECHDS'
         66935 2004-2006/PY
L76          1 (L40 OR L64) NOT 2004-2006/PY

FILE 'BIOSIS'
       1208863 2004-2006/PY
L77         46 (L41 OR L65) NOT 2004-2006/PY

FILE 'EMBASE'
       1343929 2004-2006/PY
L78         42 (L42 OR L66) NOT 2004-2006/PY

FILE 'HCAPLUS'
       3028943 2004-2006/PY
L79         45 (L43 OR L67) NOT 2004-2006/PY

FILE 'NTIS'
         33101 2004-2006/PY
L80          0 (L44 OR L68) NOT 2004-2006/PY

FILE 'ESBIOBASE'
        797821 2004-2006/PY
L81         22 (L45 OR L69) NOT 2004-2006/PY

FILE 'BIOTECHNO'
```

```
          586 2004-2006/PY
L82        26 (L46 OR L70) NOT 2004-2006/PY

FILE 'WPIDS'
       2878865 2004-2006/PY
L83           2 (L47 OR L71) NOT 2004-2006/PY

TOTAL FOR ALL FILES
L84         284 (L48 OR L72) NOT 2004-2006/PY

=> dup rem l84
PROCESSING COMPLETED FOR L84
L85           91 DUP REM L84 (193 DUPLICATES REMOVED)

=> d tot

L85  ANSWER 1 OF 91  HCAPLUS  COPYRIGHT 2006 ACS on STN
TI   Identification and Characterization of a Cell Cycle and Apoptosis
     Regulatory Protein-1 as a Novel Mediator of Apoptosis Signaling by
     Retinoid CD437
SO   Journal of Biological Chemistry (2003), 278(35), 33422-33435
     CODEN: JBCHA3; ISSN: 0021-9258
AU   Rishi, Arun K.; Zhang, Liyue; Boyanapalli, Madanamohan; Wali, Anil;
     Mohammad, Ramzi M.; Yu, Yingjie; Fontana, Joseph A.; Hatfield, James S.;
     Dawson, Marcia I.; Majumdar, Adhip P. N.; Reichert, Uwe
AN   2003:662654  HCAPLUS
DN   139:301507

L85  ANSWER 2 OF 91  SCISEARCH  COPYRIGHT (c) 2006 The Thomson Corporation  on
     STN
TI   Nutritional modulation of gene expression and homocysteine utilization by
     vitamin B-12
SO   JOURNAL OF BIOLOGICAL CHEMISTRY, (6 JUN 2003) Vol. 278, No. 23, pp.
     20778-20784.
     ISSN: 0021-9258.
AU   Oltean S; Banerjee R (Reprint)
AN   2003:490435  SCISEARCH

L85  ANSWER 3 OF 91  SCISEARCH  COPYRIGHT (c) 2006 The Thomson Corporation  on
     STN
TI   Simultaneous gene expression analysis of steady-state and actively
     translated mRNA populations from osteosarcoma MG-63 cells in response to
     IL-1 alpha via an open expression analysis platform
SO   NUCLEIC ACIDS RESEARCH, (1 SEP 2003) Vol. 31, No. 17, pp. 5157-5166.
     ISSN: 0305-1048.
AU   Ju J F (Reprint); Huang C L; Minskoff S A; Mayotte J E; Taillon B E;
     Simons J F
AN   2003:787826  SCISEARCH

L85  ANSWER 4 OF 91     MEDLINE on STN                    DUPLICATE 1
TI   Role of cysteine amino acid residues on the RNA binding activity of human
     thymidylate synthase.
SO   Nucleic acids research, (2003 Aug 15) Vol. 31, No. 16, pp. 4882-7.
     Journal code: 0411011. E-ISSN: 1362-4962.
AU   Lin Xiukun; Liu Jun; Maley Frank; Chu Edward
AN   2003372854     MEDLINE

L85  ANSWER 5 OF 91  EMBASE  COPYRIGHT (c) 2006 Elsevier B.V. All rights
     reserved on STN
TI   New Paradigms for Nutrient Control of Genome Translation
SO   Nutrition Reviews, (2003) Vol. 61, No. 12, pp. 427-431.
     Refs: 36
     ISSN: 0029-6643  CODEN: NUREA8
AU   Stover P.J.
```

AN 2004050955 EMBASE

L85 ANSWER 6 OF 91 Elsevier BIOBASE COPYRIGHT 2006 Elsevier Science B.V. on STN
AN 2003058866 ESBIOBASE
TI Correlation between clinicopathologic factors and kinetics of metabolic enzymes for 5-fluorouracil given to patients with colon carcinoma by two different dosage regimens
AU Katsumata K.; Tomioka H.; Sumi T.; Yamashita S.; Takagi M.; Kato F.; Nakamura R.; Koyanagi Y.; Aoki T.; Kato K.
CS K. Katsumata, Dept. of Digestive Tract Surgery, Hachioji Medical Center, Tokyo Medical University, 1163, Tate-machi, Hachioji, Tokyo 193-0944, Japan.
E-mail: k.katsu@col.ne.jp
SO Cancer Chemotherapy and Pharmacology, (01 FEB 2003), 51/2 (155-160), 30 reference(s)
CODEN: CCPHDZ ISSN: 0344-5704
DT Journal; Article
CY Germany, Federal Republic of
LA English
SL English

L85 ANSWER 7 OF 91 MEDLINE on STN DUPLICATE 2
TI Thymidylate synthase inhibitors as anticancer agents: from bench to bedside.
SO Cancer chemotherapy and pharmacology, (2003 Jul) Vol. 52 Suppl 1, pp. S80-9. Electronic Publication: 2003-06-18. Ref: 89
Journal code: 7806519. ISSN: 0344-5704.
AU Chu Edward; Callender Marc A; Farrell Michael P; Schmitz John C
AN 2003325728 MEDLINE

L85 ANSWER 8 OF 91 Elsevier BIOBASE COPYRIGHT 2006 Elsevier Science B.V. on STN
AN 2003214754 ESBIOBASE
TI Thymidylate synthase inhibitors as anticancer agents: From bench to bedside
AU Chu E.; Callender M.A.; Farrell M.P.; Schmitz J.C.
CS E. Chu, Cancer Center - 111D, VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516, United States.
E-mail: chueyale@yahoo.com
SO Cancer Chemotherapy and Pharmacology, Supplement, (2003), 52/1 (S80-S89), 89 reference(s)
CODEN: CCHSET ISSN: 0943-9404
DT Journal; Conference Article
CY Germany, Federal Republic of
LA English
SL English

L85 ANSWER 9 OF 91 HCAPLUS COPYRIGHT 2006 ACS on STN
TI Molecular mechanisms regulating the expression of thymidylate synthase
SO Fluoropyrimidines in Cancer Therapy (2003), 67-82. Editor(s): Rustum, Youcef M. Publisher: Humana Press Inc., Totowa, N. J.
CODEN: 69EHZZ; ISBN: 0-89603-956-0
AU Schmitz, John C.; Gollerkeri, Ashwin; Lin, Xiukun; Liu, Jun; Chu, Edward
AN 2003:615352 HCAPLUS
DN 140:245613

L85 ANSWER 10 OF 91 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI An emerging cell kinetics regulation network: Integrated control of nucleotide metabolism and cancer gene function
SO INOSINE MONOPHOSPHATE DEHYDROGENASE: A MAJOR THERAPEUTIC TARGET, (2003) Vol. 839, pp. 59-90.
ISSN: 0097-6156.

AU Sherley J L (Reprint)
AN 2003:277338 SCISEARCH

L85 ANSWER 11 OF 91 HCAPLUS COPYRIGHT 2006 ACS on STN
TI Translational regulation of thymidylate synthase and the cell cycle: Insights for clinical drug development
SO Progress in Oncology (2003) 23-45
CODEN: PORNAF; ISSN: 1535-9980
AU Schmitz, John C.; Chu, Edward
AN 2003:494196 HCAPLUS
DN 139:390460

L85 ANSWER 12 OF 91 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
TI Thymidylate synthase inhibitors as anticancer agents: From bench to bedside.
SO Cancer Chemotherapy and Pharmacology, Supplement, (2003) Vol. 52, No. 1, pp. S80-S89. .
Refs: 89
ISSN: 0943-9404 CODEN: CCHSET
AU Chu E.; Callender M.A.; Farrell M.P.; Schmitz J.C.
AN 2003350302 EMBASE

L85 ANSWER 13 OF 91 HCAPLUS COPYRIGHT 2006 ACS on STN
TI Divergent regulation of dihydrofolate reductase between malaria parasite and human host. [Erratum to document cited in CA137:103444]
SO Science (Washington, DC, United States) (2002), 297(5585), 1278
CODEN: SCIEAS; ISSN: 0036-8075
AU Zhang, Kai; Rathod, Pradipsinh K.
AN 2003:568534 HCAPLUS
DN 139:207155

L85 ANSWER 14 OF 91 MEDLINE on STN DUPLICATE 3
TI Divergent regulation of dihydrofolate reductase between malaria parasite and human host.
SO Science, (2002 Apr 19) Vol. 296, No. 5567, pp. 545-7.
Journal code: 0404511. E-ISSN: 1095-9203.
AU Zhang Kai; Rathod Pradipsinh K
AN 2002228053 MEDLINE

L85 ANSWER 15 OF 91 MEDLINE on STN DUPLICATE 4
TI Induction of thymidylate synthase as a 5-fluorouracil resistance mechanism.
SO Biochimica et biophysica acta, (2002 Jul 18) Vol. 1587, No. 2-3, pp. 194-205. Ref: 76
Journal code: 0217513. ISSN: 0006-3002.
AU Peters G J; Backus H H J; Freemantle S; van Triest B; Codacci-Pisanelli G; van der Wilt C L; Smid K; Lunec J; Calvert A H; Marsh S; McLeod H L; Bloemena E; Meijer S; Jansen G; van Groeningen C J; Pinedo H M
AN 2002341544 MEDLINE

L85 ANSWER 16 OF 91 MEDLINE on STN DUPLICATE 5
TI Thymidylate synthase as a translational regulator of cellular gene expression.
SO Biochimica et biophysica acta, (2002 Jul 18) Vol. 1587, No. 2-3, pp. 174-82. Ref: 82
Journal code: 0217513. ISSN: 0006-3002.
AU Liu Jun; Schmitz John C; Lin Xiukun; Tai Ningwen; Yan Wu; Farrell Michael; Bailly Michelle; Chen Tian min; Chu Edward
AN 2002341542 MEDLINE

L85 ANSWER 17 OF 91 MEDLINE on STN DUPLICATE 6
TI Novel aspects of resistance to drugs targeted to dihydrofolate reductase and thymidylate synthase.

SO Biochimica et biophysica acta, (2002 Jul 18) Vol. 1587, No. 2-3, pp. 164-73. Ref: 85
Journal code: 0217513. ISSN: 0006-3002.
AU Banerjee Debabrata; Mayer-Kuckuk Philipp; Capiaux Gina; Budak-Alpdogan Tulin; Gorlick Richard; Bertino Joseph R
AN 2002341541 MEDLINE

L85 ANSWER 18 OF 91 MEDLINE on STN DUPLICATE 7
TI The identification of thymidylate synthase peptide domains located in the interface region that bind thymidylate synthase mRNA.
SO Biochemical and biophysical research communications, (2002 Sep 13) Vol. 297, No. 1, pp. 24-31.
Journal code: 0372516. ISSN: 0006-291X.
AU Voeller Donna M; Zajac-Kaye Maria; Fisher Robert J; Allegra Carmen J
AN 2002461703 MEDLINE

L85 ANSWER 19 OF 91 MEDLINE on STN DUPLICATE 8
TI Effect of 2'-O-methyl antisense ORNs on expression of thymidylate synthase in human colon cancer RKO cells.
SO Nucleic acids research, (2001 Jan 15) Vol. 29, No. 2, pp. 415-22.
Journal code: 0411011. E-ISSN: 1362-4962.
AU Schmitz J C; Yu D; Agrawal S; Chu E
AN 2001094791 MEDLINE

L85 ANSWER 20 OF 91 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI Sp1 and kruppel-like factor family of transcription factors in cell growth regulation and cancer
SO JOURNAL OF CELLULAR PHYSIOLOGY, (AUG 2001) Vol. 188, No. 2, pp. 143-160. ISSN: 0021-9541.
AU Black A R (Reprint); Black J D; Azizkhan-Clifford J
AN 2001:563323 SCISEARCH

L85 ANSWER 21 OF 91 MEDLINE on STN DUPLICATE 9
TI Translational regulation as a novel mechanism for the development of cellular drug resistance.
SO Cancer metastasis reviews, (2001) Vol. 20, No. 1-2, pp. 33-41. Ref: 69
Journal code: 8605731. ISSN: 0167-7659.
AU Schmitz J C; Liu J; Lin X; Chen T M; Yan W; Tai N; Gollerkeri A; Chu E
AN 2002100734 MEDLINE

L85 ANSWER 22 OF 91 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI Human cytoplasmic serine hydroxymethyltransferase is an mRNA binding protein
SO BIOCHEMISTRY, (26 SEP 2000) Vol. 39, No. 38, pp. 11523-11531. ISSN: 0006-2960.
AU Liu X W; Reig B; Nasrallah I M; Stover P J (Reprint)
AN 2000:755418 SCISEARCH

L85 ANSWER 23 OF 91 MEDLINE on STN DUPLICATE 10
TI Comparison of thymidylate synthase (TS) protein up-regulation after exposure to TS inhibitors in normal and tumor cell lines and tissues.
SO Clinical cancer research : an official journal of the American Association for Cancer Research, (2000 Jun) Vol. 6, No. 6, pp. 2538-46.
Journal code: 9502500. ISSN: 1078-0432.
AU Welsh S J; Titley J; Brunton L; Valenti M; Monaghan P; Jackman A L; Aherne G W
AN 2001039900 MEDLINE

L85 ANSWER 24 OF 91 MEDLINE on STN DUPLICATE 11
TI Characterization of a cis-acting regulatory element in the protein coding region of thymidylate synthase mRNA.

SO Nucleic acids research, (2000 Mar 15) Vol. 28, No. 6, pp. 1381-9.
Journal code: 0411011. E-ISSN: 1362-4962.
AU Lin X; Parsels L A; Voeller D M; Allegra C J; Maley G F; Maley F; Chu E
AN 2000150253 MEDLINE

L85 ANSWER 25 OF 91 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
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L85 ANSWER 7 OF 91 MEDLINE on STN DUPLICATE 2
AB Thymidylate synthase (TS) is a folate-dependent enzyme that catalyzes the reductive methylation of 2'-deoxyuridine-5'-monophosphate to 2'-deoxythymidine-5'-monophosphate. This pathway provides the sole intracellular de novo source of 2'-deoxythymidine-5'-triphosphate; therefore, TS represents a critical target in cancer chemotherapy. 5-Fluorouracil (5-FU) was synthesized in 1957 and represents the first class of antineoplastic agents to be developed as inhibitors of TS. While 5-FU has been widely used to treat various human malignancies, its overall clinical efficacy is limited. Therefore, significant efforts have focused on the design of novel, more potent inhibitor compounds of TS. These agents fall into two main categories: folate analogs and nucleotide analogs. Five antifolate analogs are currently being evaluated in the clinic: raltitrexed, pemetrexed, nolatrexed, ZD9331, and GS7904L. Our laboratory has identified a novel mechanism of resistance that develops to TS inhibitor compounds, namely drug-mediated acute induction of new TS synthesis; this mechanism is directly controlled at the translational level. The ability of cancer cells to acutely induce the expression of TS may represent a novel mechanism for the development of cellular drug resistance. The future success of TS inhibitor compounds in the clinic may depend on novel strategies to selectively inhibit TS and on novel combination therapies to overcome cellular drug resistance.

L85 ANSWER 9 OF 91 HCAPLUS COPYRIGHT 2006 ACS on STN
AB A review on the regulation of the expression of thymidylate synthase (TS). Regulation at the level of gene amplification, transcription, translation, and post-translation are all involved in regulating the expression of TS with regard to cell-cycle-directed events, growth proliferation, and in response to exposure to cytotoxic agents.

L85 ANSWER 11 OF 91 HCAPLUS COPYRIGHT 2006 ACS on STN
AB A review. Thymidylate synthase (TS) is a folate-dependent enzyme that catalyzes the reductive methylation of 2'-deoxyuridine-5'-monophosphate (dUMP) by the reduced folate 5,10-methylenetetrahydrofolate (CH2THF) to thymidylate (dTMP) and dihydrofolate. Once synthesized, dTMP is further metabolized within the cell to the dTTP triphosphate form, an essential precursor for DNA synthesis. While dTMP can be formed through the salvage pathway, a process that is catalyzed by thymidine kinase, the TS-catalyzed reaction provides for the sole intracellular de novo source of dTMP. This reaction plays a central role in DNA biosynthesis, and given that inhibition of this reaction results in immediate cessation of cellular proliferation and growth, TS represents an important target for cancer chemotherapy. Here, the critical role of translational regulation as a mechanism for regulating TS expression is reviewed. For well over 40 yr, this enzyme served a critical catalytic function by providing essential nucleotide precursors for DNA biosynthesis. However, it is now well established that TS also serves an important role as an RNA binding

protein. Our laboratory has shown that TS binds with high affinity to its own mRNA, on the order of 1-3 nM, and directly regulates its own biosynthesis through a novel translational autoregulatory feedback mechanism. Through its role as an RNA binding protein, TS is also able to interact with several cellular mRNAs, including those corresponding to the p53 and the myc family of transcription factors. In each of these instances, TS functions as a translational repressor to coordinately regulate the expression and/or function of these important genes. Recent evidence from our group suggests that TS is an effective and potent translational regulator of cell cycle arrest, apoptosis, and chemosensitivity. The mol.-based studies outlined herein should help expand our current understanding of TS as an RNA binding protein, and they provide new insights into the role of TS as a critical regulator of certain essential aspects of cellular metabolism and intracellular signaling. Moreover, such studies are the rational basis for the future development of novel therapeutic strategies that can be used either alone or in combination with other well-established anticancer agents. Several of these therapeutic approaches are currently under development in our laboratory as well as in others in order to translate more specific and effective therapies into the clinic for the treatment of human cancers.

L85 ANSWER 15 OF 91 MEDLINE on STN DUPLICATE 4

AB Thymidylate synthase (TS) is a key enzyme in the de novo synthesis of 2'-deoxythymidine-5'-monophosphate (dTMP) from 2'-deoxyuridine-5'-monophosphate (dUMP), for which 5,10-methylene-tetrahydrofolate (CH(2)-THF) is the methyl donor. TS is an important target for chemotherapy; it is inhibited by folate and nucleotide analogs, such as by 5-fluoro-dUMP (FdUMP), the active metabolite of 5-fluorouracil (5FU). FdUMP forms a relatively stable ternary complex with TS and CH(2)THF, which is further stabilized by leucovorin (LV). 5FU treatment can induce TS expression, which might bypass dTMP depletion. An improved efficacy of 5FU might be achieved by increasing and prolonging TS inhibition, a prevention of dissociation of the ternary complex, and prevention of TS induction.In a panel of 17 colon cancer cells, including several variants with acquired resistance to 5FU, sensitivity was related to TS levels, but exclusion of the resistant variants abolished this relation. For antifolates, polyglutamylation was more important than the intrinsic TS level. Cells with low p53 levels were more sensitive to 5FU and the antifolate raltitrexed (RTX) than cells with high, mutated p53. Free TS protein down-regulates its own translation, but its transcription is regulated by E2F, a cell cycle checkpoint regulator. Together, this results in low TS levels in stationary phase cells. Although cells with a low TS might theoretically be more sensitive to 5FU, the low proliferation rate prevents induction of DNA damage and 5FU toxicity. TS levels were not related to polymorphisms of the TS promoter. Treatment with 5FU or RTX rapidly induced TS levels two- to five-fold. In animal models, 5FU treatment resulted in TS inhibition followed by a two- to three-fold TS induction. Both LV and a high dose of 5FU not only enhanced TS inhibition, but also prevented TS induction and increased the antitumor effect. In patients, TS levels as determined by enzyme activity assays, immunohistochemistry and mRNA expression, were related to a response to 5FU. 5FU treatment initially decreased TS levels, but this was followed by an induction, as seen with an increased ratio of TS protein over TS-mRNA. The clear retrospective relation between TS levels and response now forms the basis for a prospective study, in which TS levels are measured before treatment in order to determine the treatment protocol.

L85 ANSWER 16 OF 91 MEDLINE on STN DUPLICATE 5

AB Studies from our laboratory have shown that the folate-dependent enzyme, thymidylate synthase (TS), functions as an RNA binding protein. There is evidence that TS, in addition to interacting with its own TS mRNA, forms a ribonucleoprotein complex with a number of other

cellular mRNAs, including those corresponding to the p53 tumor suppressor gene and the myc family of transcription factors. Using both in vitro and in vivo model systems, we have demonstrated that the functional consequence of binding of TS protein to its own cognate mRNA, as well as binding of TS to the p53 mRNA, is translational repression. Herein, we review current work on the translational autoregulatory control of TS expression and discuss the molecular elements that are required for the TS protein-TS mRNA interaction. TS may play a critical role in regulating the cell cycle and the process of apoptosis through its regulatory effects on expression of p53 and perhaps other cell cycle related proteins. Finally, the ability of TS to function as a translational regulator may have important consequences with regard to the development of cellular resistance to various anticancer drugs.

L85 ANSWER 17 OF 91 MEDLINE on STN DUPLICATE 6
AB Drug resistance is often a limiting factor in successful chemotherapy. Our laboratory has been interested in studying mechanisms of resistance to drugs that are targeted to the thymidylate biosynthesis pathway especially those that target thymidylate synthase (TS) and dihydrofolate reductase (DHFR). We have used leukemia as a model system to study resistance to methotrexate (MTX) and colorectal cancer as the model system to study 5-fluorouracil (5-FU) resistance. In leukemias, we and others have shown that transport, efflux, polyglutamylation and hydrolase activities are major determinants of MTX resistance. We have further reported that some leukemic cells have an increase in DHFR gene copy number possibly contributing to the resistant phenotype. Recently, we have begun to study in detail the molecular mechanisms that govern translational regulation of DHFR in response to MTX as an additional resistance mechanism. Studies thus far involving colorectal tumors obtained from patients have focused predominantly on the predictive value of levels of TS expression and p53 mutations in determining response to 5-FU. Although the predictive value of these two measures appears to be significant, given the variety of resistance to 5-FU observed in cell lines, it is not likely that these are the only measures predictive of response or responsible for acquired resistance to this drug. The enzyme uridine-cytidine monophosphate kinase (UMPK) is an essential and rate-limiting enzyme in 5-FU activation while dihydropyrimidine dehydrogenase (DPD) is a catabolic enzyme that inactivates 5-FU. Alterations in UMPK and DPD may therefore explain failure of 5-FU response in the absence of alterations in TS or p53. Transcription factors that regulate TS may also influence drug sensitivity. We have found that mRNA levels of the E2F family of transcription factors correlates with TS message levels and are higher in lung metastases than in liver metastases of colorectal cancers. Moreover, gene copy number of the E2F-1 gene appears to be increased in a significant number of samples obtained from metastases of colorectal cancer. We have also generated mutants of both DHFR and TS that confer resistance to MTX as well as 5-FU by random as well as site-directed mutagenesis. These mutants used alone or as fusion cDNAs of the mutants have proven to be useful in transplant studies where transfer of these mutant cDNAs to bone marrow cells have been shown to confer drug resistance to recipients. The fusion cDNAs of DHFR such as the DHFR-herpes simplex virus type 1 thymidine kinase (HSVTK) are also useful for regulation of gene expression in vivo using MTX as the small molecule regulator that can be monitored by positron emission tomography (PET) scanning or by optical imaging using a fusion construct such as DHFR-EGFP.

L85 ANSWER 18 OF 91 MEDLINE on STN DUPLICATE 7
AB Thymidylate synthase (TS) is a critical chemotherapeutic target and intracellular levels of TS are an important determinant of sensitivity to TS inhibitors. Translational autoregulation represents one cellular mechanism for controlling the level of expression of TS. This mechanism involves the binding of TS protein to its own messenger RNA (mRNA), thus, repressing translational

efficiency. The presence of excess substrate or inhibitors of TS leads to derepression of protein binding to mRNA, resulting in increased translational efficiency and ultimately increased levels of TS protein. TS protein has been shown to bind to two distinct areas on its mRNA. The goal of the present work is to define the TS domains responsible for this interaction. Using a separate series of overlapping 17-mer peptides spanning the length of both the human and Escherichia coli TS sequences, we have identified six potential domains located in the interface region of the TS protein that bind TS mRNA. The identified domains that bind TS mRNA include three concordant regions in both the human and E. coli peptide series. Five of the six binding peptides contain at least one invariant arginine residue, which has been shown to be critical in other well-defined protein-RNA interactions. These data suggest that the identified highly conserved protein domains, which occur at the homodimeric interface of TS, represent potential participating sites for binding of TS protein to its mRNA.

L85 ANSWER 19 OF 91 MEDLINE on STN DUPLICATE 8
AB Translation of thymidylate synthase (TS)
mRNA is controlled by its own protein end-product TS in a negative autoregulatory manner. Disruption of this regulation results in increased synthesis of TS and may lead to the development of cellular drug resistance to TS-directed anticancer agents. As a strategy to inhibit TS expression, antisense 2'-O-methyl RNA oligoribonucleotides (ORNs) were designed to directly target the 5' upstream cis-acting regulatory element (nucleotides 80-109) of TS mRNA. A 30 nt ORN, HYB0432, inhibited TS expression in human colon cancer RKO cells in a dose-dependent manner but had no effect on the expression of beta-actin, alpha-tubulin or topoisomerase I. TS expression was unaffected by treatment with control sense or mismatched ORNs. HYB0504, an 18 nt ORN targeting the same core sequence, also repressed expression of TS protein. However, further reduction in oligo size resulted in loss of antisense activity. Following HYB0432 treatment, TS protein levels were reduced by 60% within 6 h and were maximally reduced by 24 h. Expression of p53 protein was inversely related to that of TS, suggesting that p53 expression may be directly linked to intracellular levels of TS. Northern blot analysis demonstrated that TS mRNA was unaffected by HYB0432 treatment. The half-life of TS protein was unchanged after antisense treatment suggesting that the mechanism of action of antisense ORNs is mediated through a process of translational arrest. These findings demonstrate that an antisense ORN targeted at a critical cis-acting element on TS mRNA can specifically inhibit expression of TS protein in RKO cells.

L85 ANSWER 21 OF 91 MEDLINE on STN DUPLICATE 9
AB Cellular drug resistance is one of the principal obstacles to the clinical efficacy of cancer chemotherapy. In this review, we describe the potential role for translational regulation as a novel mechanism for modulating chemosensitivity. The evidence for the translational control of thymidylate synthase, dihydrofolate reductase, and p53 will be presented, as will experimental data showing how disruptions in this important regulatory process can lead to the rapid emergence of cellular drug resistance.

L85 ANSWER 23 OF 91 MEDLINE on STN DUPLICATE 10
AB Thymidylate synthase (TS) is an important target for cancer chemotherapy. However, several mechanisms of resistance to TS inhibitors have been described. One mechanism that may be relevant to short-term exposure to TS inhibitors occurs as a result of disruption of the autoregulatory loop, which allows TS to control its own translation. This disruption leads to up-regulation of TS protein and is generally thought to decrease efficacy. This study has investigated TS protein up-regulation using a range of TS inhibitors in both tumor and nonmalignant cell lines in vitro and in vivo. Up-regulation of TS protein showed a time-, dose-, and cell-type-specific

response to treatment with ZD9331. This response was observed in W1L2 cells treated for 24 h at equitoxic doses of raltitrexed (6-fold), ZD9331 (10-fold), fluorouracil (5-fold), LY231514 (7-fold), AG337 (7-fold), and BW1843U89 (3-fold). Up-regulation was observed over a range of doses. Elevation of TS protein only persisted up to 12 h after removal of drug. The extent of induction does not depend on basal TS levels. Nontransformed human fibroblasts showed significantly greater up-regulation of TS protein than tumor cells exposed to an equitoxic dose of ZD9331. In vivo experiments using the L5178Y thymidine kinase -/- mouse lymphoma implanted into DBA2 mice also showed greater up-regulation of TS protein in normal intestinal epithelial cells compared with tumor cells. These results confirm that TS up-regulation is a common feature of TS inhibition in tumor cells and that it may occur to a greater extent in normal tissues, although the clinical implications of these findings remain to be determined.

L85 ANSWER 27 OF 91 HCAPLUS COPYRIGHT 2006 ACS on STN
AB Unavailable

L85 ANSWER 28 OF 91 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 13
AB Thymidylate synthase (TS) is indispensable in the de novo synthesis of dTMP. As such, it has been an important target at which anti-neoplastic drugs are directed. The fluoropyrimidines 5-fluorouracil and 5-fluoro-2'- deoxyuridine are cytotoxic as a consequence of inhibition of TS by the metabolite 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP). This inhibition occurs through formation of a stable ternary complex among the enzyme, the nucleotide analog, and the co-substrate N5,N10-methylenetetrahydrofolate. Numerous studies have shown that cellular concentrations of TS undergo about a 2-4-fold induction following treatment with TS inhibitors. An extensive body of in vitro studies has led to the proposal that this induction occurs because of relief of the translational repression brought on by the binding of TS to its own mRNA. In the current study, we have tested several predictions of this autoregulatory translation model. In contrast to expectations, we find that fluoropyrimidines do not cause a change in the extent of ribosome binding to TS mRNA. Furthermore, mutations within the mRNA that abolish its ability to bind TS have no effect on the induction. Finally, enzyme turnover measurements show that the induction is associated with an increase in the stability of the TS polypeptide. Our results, in total, indicate that enzyme stabilization, rather than translational derepression, is the primary mechanism of TS induction by fluoropyrimidines and call into question the general applicability of the autoregulatory translation model.

L85 ANSWER 33 OF 91 HCAPLUS COPYRIGHT 2006 ACS on STN
AB A review with 63 refs. of the title topic with the following sections: gene amplification of thymidylate synthase, transcriptional regulation of thymidylate synthase, translational regulation of thymidylate synthase, interaction of thymidylate synthase with cellular RNAs. The conclusion from the review follows. Thymidylate synthase (TS) plays a central role in the biosynthesis of thymidylate, an essential precursor for DNA biosynthesis. It is well-established that transcriptional, posttranscriptional, and translational events are all involved in regulating TS expression as it relates to cell-cycle-associated events and growth proliferation. With regard to the mechanisms underlying the expression of TS in response to chronic drug exposure, gene amplification and enhanced transcription have been shown to play major roles. Translational regulation appears to be the principle mechanism underlying the acute expression of TS in response to treatment with various TS inhibitor compds. The ability to increase the expression of TS in response to growth stimuli and/or to exposure to cytotoxic agents either on an acute or chronic basis serves as an

important adaptive response mechanism that allows for normal cellular synthetic function to be maintained. Recent investigations have shown that in addition to its well-established role in enzyme catalysis, TS can also function as an RNA-binding protein. In this capacity, TS can regulate its own synthesis and that of other critical cellular genes at the translational level (see Fig. 1). Clearly, an enhanced understanding of each of these basic regulatory events should provide new insights as to how the expression of TS is controlled. Moreover, these mol.-based investigations may provide important leads for the rational design and development of novel therapeutic approaches that aim to inhibit TS expression.

L85 ANSWER 35 OF 91 MEDLINE on STN DUPLICATE 16
AB The translational initiation codon for thymidylate synthase (TS) mRNA is located in a unique stem-loop structure which contains an internal cytosine-cytosine (CC) bubble. This stem-loop structure is thought to be important in the regulation of TS translation, which is itself an important target for anticancer drugs, such as 5-fluorouracil. Internal bubble or bulge structures are candidate receptors for the aminoglycoside antibiotics. It is shown here that aminoglycosides bind in a specific and saturable fashion with dissociation constants of approximately 1 microM to a TS mRNA site 1 construct and that the binding site for the aminoglycosides is located in the CC bubble region. In fact, the CC bubble, when grafted into other stem-loop structures, confers aminoglycoside binding on them. These studies reveal an additional binding domain for aminoglycosides and also suggest how novel anti-cancer drugs might be designed that affect TS mRNA translation rather than enzyme function.

L85 ANSWER 42 OF 91 HCAPLUS COPYRIGHT 2006 ACS on STN
AB A review with 103 refs. The topics include thymidylate synthase (TS) activity and cell proliferative activity, cell cycle-dependent regulation of TS mRNA levels, autoregulation of TS mRNA translation, and TS as a metabolic enzyme binding c-myc and p53 mRNAs.

L85 ANSWER 50 OF 91 HCAPLUS COPYRIGHT 2006 ACS on STN
AB A review, with 70 refs., discussing exptl. evidence characterizing the mol. elements underlying the translational regulation of thymidylate synthase. Evidence is presented demonstrating the interaction of thymidylate synthase with various cellular mRNA species critically involved in the cell cycle and a model is proposed whereby thymidylate synthase may play an essential role as a regulator of cellular metabolism

L85 ANSWER 54 OF 91 MEDLINE on STN DUPLICATE 22
AB Continuous infusions of 5-fluorouracil (5-FU) are increasingly used in the treatment of cancer. Their optimal use, however, has still to be determined since the availability of suitable animal models is limited. We studied continuous infusions in mice using subcutaneously implanted pellets that release 5-FU over a period of 3 weeks. At the maximum tolerated dose (MTD) (based on the systemic toxicity in healthy animals) we assessed the antitumour activity, haematological toxicity, inhibition of thymidylate synthase (TS) in tumours and the concentration of 5-FU in plasma during the 3-week period. We also studied the addition of leucovorin in different schedules. The dose-limiting toxicity was weight loss, and at the MTD of 10 mg of 5-FU released in 21 days per mouse myelosuppression was tolerable (nadir for leucocytes and thrombocytes was approximately 40% of pretreatment levels). In several independent experiments using the 5-FU-resistant Colon 26 tumour, a good antitumour activity was observed during the first part of the infusion, but thereafter the growth of the tumours resumed; the overall effect of continuous infusions was thus comparable to that of bolus injections. Coadministration of leucovorin did not enhance the therapeutic results; depending on the schedule used, it proved ineffective or only increased

toxicity. Similar results were obtained with head and neck squamous cell carcinomas and with the 5-FU-sensitive tumour Colon 38. In Colon 26 tumours the TS activity (FdUMP-binding assay) initially decreased to 20-30% of controls and returned to normal after 11 days. In the catalytic TS assay a slight inhibition was observed for the continuous infusion, followed after 11 days by a marked (4-fold) increase in activity. 5-FU plasma levels varied from 0.1 to 1 microM following a circadian rhythm (with a peak at 6 h after light onset), and were maintained during the entire period. Subcutaneously implanted pellets represent a suitable model to study prolonged administration of 5-FU in mice and to evaluate the effect of modulating agents in laboratory animals before transferring data obtained in vitro to the clinic.

L85 ANSWER 55 OF 91 MEDLINE on STN DUPLICATE 23
AB Previous studies have shown that human TS mRNA translation is controlled by a negative autoregulatory mechanism. In this study, an RNA electrophoretic gel mobility shift assay confirmed a direct interaction between Escherichia coli (E.coli) TS protein and its own E.coli TS mRNA. Two cis-acting sequences in the E.coli TS mRNA protein-coding region were identified, with one site corresponding to nucleotides 207-460 and the second site corresponding to nucleotides 461-807. Each of these mRNA sequences bind TS with a relative affinity similar to that of the full-length E.coli TS mRNA sequence (IC50 = 1 nM). A third binding site was identified, corresponding to nucleotides 808-1015, although its relative affinity for TS (IC50 = 5.1 nM) was lower than that of the other two cis-acting elements. E.coli TS proteins with mutations in amino acids located within the nucleotide-binding region retained the ability to bind RNA while proteins with mutations at either the nucleotide active site cysteine (C146S) or at amino acids located within the folate-binding region were unable to bind TS mRNA. These studies suggest that the regions on E.coli TS defined by the folate-binding site and/or critical cysteine sulfhydryl groups may represent important RNA binding domains. Further evidence is presented which demonstrates that the direct interaction with TS results in in vitro repression of E.coli TS mRNA translation.

L85 ANSWER 56 OF 91 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 24
AB Translational regulation of mRNA is an important step in the control of gene expression. In a general way, the efficiency of the translational apparatus can be influenced either positively or negatively by changing the level or the activity of rate-limiting protein factors taking part in the process of translation. But translational control can also be very specific, affecting only a single mRNA or class of mRNA molecules. In most of these cases regulation takes place at the level of initiation of translation, which is often attributable to structural peculiarities of the mRNA in question, especially of the 5'-untranslated region or leader. This review summarizes the mechanisms which lie at the root of translational control. A better understanding of these mechanisms will eventually provide us with new drugs and antisense oligonucleotide technology, aimed at influencing the level of expression of single proteins. These developments are of interest to basic researchers and clinicians alike, because they may profoundly change the ways in which we treat, e.g. viral infections and malignancies in the future.

L85 ANSWER 59 OF 91 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

L85 ANSWER 63 OF 91 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 27
AB Human thymidylate synthase (TS) protein specifically binds to its own TS mRNA and functions as a translational repressor. In

the presence of reducing agents, the RNA binding activity of TS protein is significantly enhanced. In contrast, treatment of TS protein with the oxidizing agent diamide inhibits RNA binding. Scatchard analysis reveals that in the presence of the reducing agent 2-mercaptoethanol, the TS protein/TS mRNA interaction changes from low (K(d) = 66 nM) to high (K(d) = 2.6 nM) apparent affinity. The catalytic activity of TS is increased by up to 6.5-fold in the presence of 2- mercaptoethanol. These studies demonstrate that the interaction between TS protein and its target TS mRNA is sensitive to the presence of reducing reagents and is dependent upon a reversible sulfhydryl switch mechanism.

L85 ANSWER 64 OF 91 MEDLINE on STN DUPLICATE 28
AB This review will focus on cases of specific translational control by protein/RNA interactions in the 5'- or 3'-UTR of eukaryote mRNA where either the cis-acting RNA determinant or the trans-acting protein (or preferably both) have been identified with fair certainty. Examples of messages that are regulated by 5' motifs, which are proposed to occlude ribosome binding when bound by their specific factors, include ferritin and ribosomal protein mRNAs and the autoregulated thymidylate synthase and poly(A)-binding mRNAs. However, it has become increasingly evident recently that 3' UTR determinants and their specific binding proteins also regulate translation efficiency either directly, or indirectly via an influence on the polyadenylation status of the mRNA. It is still unclear how events at the 3' end of mRNA influence ribosome binding. Most, if not all, of the mRNAs known to be regulated by 3' UTR motifs are subject to regulation during early development or during differentiation such as several spermatocyte and oocyte mRNAs and erythroid lipoxygenase mRNA. To date, in all cases where translation is controlled directly by specific protein/mRNA interactions, the protein seems to act as a negative regulator, a translational repressor, whose binding to the specific site on the mRNA results in inhibition of initiation. The only cases of translational activation known so far concern internal initiation of translation of picornaviral RNAs, but this topic is beyond the scope of this review.

L85 ANSWER 65 OF 91 MEDLINE on STN DUPLICATE 29
AB Thymidylate synthase (TS) is an essential enzyme that catalyzes the formation of thymidylic acid in the de novo biosynthetic pathway and is the target enzyme for a variety of chemotherapeutic agents. The TS gene is expressed at a much higher level in proliferating cells than in quiescent cells. Control is primarily exerted at the posttranscriptional level. Studies with chimeric TS minigenes have shown that regulation of TS mRNA content in growth-stimulated mouse fibroblasts requires the presence of sequences located upstream of the essential promoter elements. In addition, an efficiently spliced intron must be present within the transcript. Neither sequence by itself is sufficient for proper regulation, suggesting that the upstream and downstream sequences may communicate to effect regulation. A possible mechanism by which the upstream sequences influence the efficiency of splicing of TS transcripts in a cell cycle specific manner is described. Expression of the human TS gene is also controlled at the translational level. The TS enzyme is able to block the translation of its own mRNA by binding to the message in the vicinity of the AUG start codon. The translational block is relieved in the presence of substrates or inhibitors of the enzyme. The autogenous translational regulation of TS mRNA is likely to be responsible for the rapid increase in TS enzyme level that occurs when cells are exposed to certain TS inhibitors. Elucidation of the mechanism by which the translational control is exerted may lead to the design of more effective TS inhibitors.

L85 ANSWER 67 OF 91 MEDLINE on STN DUPLICATE 30
AB Translation of thymidylate synthase (TS) mRNA is controlled by its own protein product, TS, in an

autoregulatory manner. Direct binding of TS protein to two different cis-acting elements on the TS mRNA is associated with this translational regulation. In this study, an immunoprecipitation-reverse transcription-PCR technique was used to identify a TS ribonucleoprotein (RNP) complex in cultured human colon cancer cells. Using antibodies specific for TS protein, we show that TS is complexed in vivo with its own TS RNA. Furthermore, evidence demonstrating a direct interaction between the mRNA of the nuclear oncogene c-myc and TS protein is presented.

L85 ANSWER 68 OF 91 MEDLINE on STN DUPLICATE 31
AB In vitro transcribed thymidylate synthase (TS) mRNA which is 100% substituted with 5-fluorouracil (FUra) was analyzed for changes in mRNA secondary structure, for alterations in translational efficiency, and for evidence of translational miscoding in vitro. FUra substitution in TS mRNA results in an altered migration pattern in non-denaturing RNA gels and in decreased hyperchromicity in RNA melting temperature studies, consistent with a change in mRNA secondary structure. However, no change in the translational efficiency of FUra-substituted TS mRNA is seen compared to control TS mRNA in either rabbit reticulocyte lysate or wheat germ extract in vitro translation systems. Analysis of the in vitro translation product of FUra-substituted TS mRNA by Western immunoblotting, isoelectric focusing, 5-fluoro-2'-deoxyuridine 5'-monophosphate binding, and TS catalytic activity experiments shows no difference compared to control TS mRNA. We conclude that the in vitro translation products of FUra-substituted and control TS mRNA are identical. Our findings do not support the hypothesis that changes in the mRNA template are responsible for the RNA-directed cytotoxicity of FUra.

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AB We have investigated the mechanism of inactivation of thymidylate synthase (TS) by ICI D1694 (a folate-based quinazoline) in normal versus tumor- derived human mammary epithelial cells. ICI D1694 is a very potent cytotoxic agent against these cells with IC50 values of 1-2 nM. Its growth inhibitory activity was completely reversed by the addition of thymidine, confirming that TS is its sole target in these cells. Remarkably, TS protein levels rose by 10-40-fold following treatment with ICI D1694, depending on cell type, while TS mRNA levels remained constant. The mechanism appears to be a release of 'detainment' of TS translation, since addition of cycloheximide, a translational inhibitor, blocked the TS protein levels from rising. But coadministration of 5,6-dichlorobenzimidazole, a transcriptional inhibitor, did not overcome protein accumulation, nor did thymidine which overcomes growth inhibition by ICI D1694. 5,10-Methylenetetrahydrofolate (via folinic acid), however, did block the effects of ICI D1694, showing that the drug has its effect upon both detainment and enzyme inhibition by binding to the folate substrate site of TS. In addition, in the presence of ICI D1694, TS protein was no longer cell cycle-regulated as evident by its constitutive expression in synchronized cells. This accumulation and constitutive expression of TS induced by D1694 should increase drug resistance under a clinical setting. We suggest that an ideal inhibitor of TS would target the TS allosteric site that binds to TS mRNA, responsible for specific translation of the protein, thereby complimenting inactivation of the enzyme.

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L85 ANSWER 79 OF 91 LIFESCI COPYRIGHT 2006 CSA on STN DUPLICATE 36
AB Human thymidylate synthase appears to regulate its own synthesis by repressing translation of thymidylate synthase mRNA.

L85 ANSWER 80 OF 91 MEDLINE on STN DUPLICATE 37
AB Thymidylate synthase (TS; 5,10-methylenetetrahydrofolate:dUMP C-methyltransferase, EC 2.1.1.45) is essential for the de novo synthesis of thymidylate, a precursor of DNA. Previous studies have shown that the cellular level of this protein is regulated at both the transcriptional and posttranscriptional levels. The regulation of human TS mRNA translation was studied in vitro with a rabbit reticulocyte lysate system. The addition of purified human recombinant TS protein to in vitro translation reactions inhibited translation of TS mRNA. This inhibition was specific in that recombinant TS protein had no effect on the in vitro translation of mRNA for human chromogranin A, human folate receptor, preplacental lactogen, or total yeast RNA. The inclusion of dUMP, 5-fluoro-dUMP, or 5,10-methylene-tetrahydrofolate in in vitro translation reactions completely relieved the inhibition of TS mRNA translation by TS protein. Gel retardation assays confirmed a specific interaction between TS protein and its corresponding mRNA but not with unrelated mRNAs, including human placenta, human beta-actin, and yeast tRNA. These studies suggest that translation of TS mRNA is controlled by its own protein end product, TS, in an autoregulatory manner.

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